REMARKS

Claims 1-24 are pending. Claims 19-24 are withdrawn as being drawn to non-elected inventions. Claims 1-18 are being examined. Upon entry of the foregoing amendment claims 1-24 are hereby canceled and new claims 25-45 are added. Applicants assert that subject matter encompassed by new claims 25-45 largely reflects that of the canceled claims and the subject matter disclosed throughout the specification, e.g., pages 8-22 and Examples 1-8. Accordingly, Applicants earnestly believe that new claims 25-45 do not comprise new matter.

Specifically, support for claims 25-35 is found throughout the specification, e.g., page 12, line 27 to page 18, line 7. Support for claims 36-45 is found on page 19, lines 22-31.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 3-5, 13-15 and 18 had been objected to under 37 CFR 1.75(c) as allegedly in improper form because a multiple dependent claim should refer to other claim. It is respectfully submitted that upon entry of the foregoing amendment, the instant objection is hereby rendered moot.

Claims 1-18 had been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is respectfully submitted that the cancellation of pending claims 1-24 removes the allegedly offending language that Examiner cites in support of the instant rejection. In addition, the allegedly offending language is absent from newly added claims 25-45. Accordingly, it is respectfully submitted that upon entry of the foregoing amendment, the instant rejection is overcome.

Claims 1-18 had been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Vold et al. (U.S. Pat. No.: 5,561,049) ("Vold"), in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30,(1996)) ("Da Costa"), and further in view of Hoier-Madsen et al., (Int. J. Tiss Reac. Xl (6), 327-332 (1989)) (Hoier-Madsen"). Claims 1-10 had also been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Neurath AR, (U.S. Pat. No. 4,459,539) ("Neurath"), in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30,(1996)) ("Da Costa"), and further in view of Hoier-Madsen et al., (Int. J. Tiss Reac. Xl (6), 327-332 (1989)) (Hoier-Madsen").

Rejection of Claims 1-18 Under 35 USC § 103(a) Over Vold in view of Da Costa and further in view of Hoier-Madsen

Claims 1-18 had been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Vold et al. (U.S. Pat. No.: 5,561,049) ("Vold"), in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30,(1996) ("Da Costa"), and further in view of Hoier-Madsen et al., (Int. J. Tiss Reac. Xl (6), 327-332 (1989) (Hoier-Madsen").

The Examiner alleges that claims 1-18 are unpatentable under 35 USC § 103(a) over the combined teachings of Vold, taken in view of Da Costa and further in view of Hoier-Madsen.

The Examiner further alleges that Vold et al. teach methods of determining the presence or amount of antibodies in a sample suspected of containing the antibodies. One of the methods relates to the use of a first binding agent that binds the complex and does not bind the antigen when the antigen is not part of the complex, and to the use of a second binding agent that selectively binds the antigen relative to binding the complex when the complex is bound to the

first binding agent. As an example of Vold's method, the Examiner refers to Vold method of detecting auto-antibodies to insulin and glutamic acid decarboxylase ("GAD").

The Examiner concludes that in view of the high level of skill existent in the art at the time that the invention was made, that arriving at the claimed subject matter is considered to be routine optimization of the specific conditions of Vold. Such routine optimization is alleged to include choosing pH conditions for binding and dissociation, or the choice of labels for the molecular indicators of immune complex formation.

The Examiner further alleges that Da Costa et al. purified and characterized a folate binding protein from placenta whereas Hoier-Madsen teach the existence of serum antibodies to a folate binding protein in cows milk.

Applicants respectfully submit that the combination of references cited above do not establish a prima facie case of obviousness of either canceled claims 1-18 or newly added claims 25-45. The primary reference, Vold, does not disclose conditions or methods suitable to be used in the claimed method in view of the fact that Vold does not identify antibodies in a sample by detecting antigen-antibody complexes. See Vold, col. 7, lines 27-29. In fact, Vold's methodology operates under a completely different concept. Instead, Vold teaches an assay for antibodies in a sample based upon measuring the amount of antigen added to the sample in order to begin identifying free antigen. By focusing on detecting very small quantities of antibodies Vold's method suffers from the drawback that it cannot be employed to analyze samples with high concentrations of antibodies. Vold, col. 7, lines 42-47. Therefore, the concept of antibody detection is substantially different from that described in the claims.

Further, a critical feature of Vold's method is the use of a first binding agent that recognizes the antigen-antibody complex but does not recognize the free antigen; and a second

binding agent that preferentially recognizes free antigen relative to the antigen in the immune complex. (See col. 3, lines 47-57; and col 8, line 66 to col. 9, line 26).

Applicants respectfully submit that Vold's method is unrelated to the claimed subject matter, as well as the methodology used in da Costa. It is respectfully brought to the Examiner's attention that there is no disclosure in da Costa even remotely relating to Vold's concept. In fact, da Costa clearly teaches away from Vold in that identifying and purifying preparative amounts of antibodies is performed under conditions in which substantially high antibody concentrations are evident. This directly contradicts Vold explicitly limiting their method to samples of very low antibody concentration. Accordingly, Vold taken in combination with da Costa is insufficient to establish a prima facie case of obviousness. MPEP 2143.01 (V) (citing In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.").

It is further respectfully submitted that the proposed modifications underlying the Office Action would require a substantial modification of Vold's concept. For example, the method of identifying antibodies by assaying for free antigen and the use of Vold's specified first and second binding agents are not encompassed by the claimed method. Accordingly, Vold taken individually or in combination with da Costa is insufficient to establish a prima facie case of obviousness. See MPEP 2143.01 (VI) (citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.").

Therefore, it is respectfully submitted that it is highly unlikely that persons of ordinary

skill in the art would be motivated to modify the teachings of Vold according to the disclosures of Da Costa, and further in view of Hoier-Madsen, to arrive at the subject matter of canceled claims 1-18, or newly added claims 25-45

Accordingly, it is respectfully requested that the rejection over Vold in view of da Costa and further in view of Hoier-Madsen be withdrawn.

Rejection of Claims 1-10 Under 35 USC § 103(a) Over Neurath in view of Da Costa and further in view of Hoier-Madsen

Claims 1-10 had also been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Neurath AR, (U.S. Pat. No. 4,459,539) ("Neurath"), in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30,(1996)) ("Da Costa"), and further in view of Hoier-Madsen et al., (Int. J. Tiss Reac. Xl (6), 327-332 (1989)) (Hoier-Madsen").

The Examiner alleges that Neurath teaches a process for determining the presence of an antigen or antibody in a sample wherein said antigen or antibody exists in the form of an immune complex comprising, dissociating an immune complex with a dissociating buffer, removing the dissociating buffer and contacting the dissociated immune complex with a solid support. The support is then probed with either a radioactive ligand or antibody. The Examiner then concludes that it would have been obvious for a person of ordinary skill in the art to have optimized and adjusted the conditions of Neurath to detect antibodies against FRs as taught by Hoier-Madsen et al. in the light of the characteristics of folate receptors as taught by da Costa et al with an expectation of success. See Neurath, Abstract, or col. 2, lines 30-55 for a general recitation of the method's steps.

Applicants respectfully submit that Neurath's methodology is significantly different from that encompassed by the claimed subject matter. In addition, it is difficult to understand how da

Costa provides anything more than the purification of an antibody to FR.

Neurath's method is a general method directed to detecting a purified antigen (Example 2) or an antigen present within purified and dissociated immune complexes (Examples 3 and 4). Accordingly, Neurath does not disclose any method in which a specific antibody is identified. Moreover, it is respectfully submitted that the Neurath method would not work in relation to the claimed invention. For example, it is unlikely that many if not all variable domains become irreversibly non-functional given the denaturing conditions – attaching to a support and denatured at low or high pH (Neurath, col. 4, lines 1-12). It is well-known in many cases that immobilizing proteins on a substrate often prevents re-establishing the protein's function as it is constrained by the support.

However, as is known and confirmed by Neurath this problem is far less serious when it is the antigen that is immobilized on the support and the support is probed with antibody. This difference in sensitivity is due to the fact that whereas the immobilized antibody must be in a functional conformation to be probed by an antigen, this is not the case for detecting antigen by probing with antibody. The antigen's only "function" in the assay is to provide epitopes for the antibody to bind. Therefore, being irreversibly denatured actually enhances the antigen's role This is why it is common practice to immunize animals with denatured polypeptide antigens.

Another major difference between the method of the present invention and that of Neurath is that the starting material for Neurath's assay is purified immune complexes. In a sense, Neurath's assay begins at point where Applicants' method ends, the formation of immune complexes for detection. Accordingly, the proposed modification of Neurath, i.e., to not start with purified immune complexes, in order to reach the claimed subject matter. Such a modification would clearly alter the principle of Neurath's method and render it unsuitable for

his own purpose, thereby running counter to the guidelines and case law set out in MPEP 2143.01 (V) and (VI) (see above).

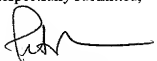
Similarly, there is no step in the claimed subject matter encompassing the step of attaching an immune complex to a support, followed by completely dissociating the immune complex from the support and dissociating the immune complex into component antigen and antibody (Neurath, col. 4, lines 34-36). Such a step is unnecessary and provides additional reagents, time and cost to the consumer. Further, the step would have to be placed after the last step in the claimed method further underscoring the large gap in the concepts underlying Neurath and the claimed method.

Therefore, it is highly unlikely that persons of ordinary skill in the art would be motivated to modify the teachings of Neurath according to the disclosures of da Costa and Hoier-Madsen, in order to arrive at the claimed subject matter. In addition, as discussed above, it is unlikely that Neurath's method can be adapted to measure or identify antibodies by probing with antigen.

It is respectfully submitted that the cited references do not teach or suggest the claimed subject matter, and therefore are insufficient to establish a *prima facie* case of obviousness. Accordingly, withdrawal of all rejections under 35 U.S.C. § 103(a) is respectfully requested.

It is respectfully submitted that the foregoing amendments and remarks effectively address each of the issues underlying the Examiner's rejections. It is therefore respectfully suggested that the claims are in condition for allowance, and that allowance is respectfully requested.

Respectfully submitted,



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